-- 35. (New) A method of treating a bone disorder in a patient which comprises implanting in the patient a substrate as claimed in claim 26. --

B6 cont. 36. (New) A method of delivering pharmaceutically active compounds to a patient which comprises implanting in the patient a substrate as claimed in claim 26 comprising one or more pharmaceutically active compounds. --

REMARKS

The Examiner has correctly indicated that process claim 17 relates to the non-elected group 2 invention. Claim 17 has, therefore, properly been excluded from prosecution. However, it is respectfully submitted that claims 18 to 20 which the Examiner has excluded also should be retained now that claim 18 depends only on claim 16 (not claim 17) i.e. so that these subsidiary claims 18 to 20 are only dependent on the vesicle process claim 16.

Claims Rejections - 35 U.S.C. §112

Claims 9 to 15, 26 to 30, 32 and 33 stand rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Examiner points out that for "droplet" in claims 9 to 15 and 26 there is no antecedent basis in claim 1. Accordingly, this word has been excluded from these claims (and also claim 27).

The Examiner considers that the wording of claim 14 is unclear as to how the encapsulated pharmaceutically active agent can assist the binding of the vesicle. This claim 14 has been amended to indicate clearly the nature of the pharmaceutically active compound rather than its disposition

The Examiner also believes that it is unclear as to what is meant by "electrically conducting and non conducting regions on its surface" in claim 27 and likewise in claims 28 and 29. Claim 27 has therefore been amended to indicate that there is present a surface layer comprising electrically conducting and non conducting regions with a layer comprising vesicles on the conducting regions.

It is believed, therefore, that the amendments made in response to the Examiner's comments render the claims in question clear.

Claims 32 and 33 stand rejected under 35 U.S.C. § 101. These claims have been replaced by claims which are more appropriate under U.S. practice, namely method claims as set out in new claims 34 and 35.

Further, to meet a potential objection, claims 24 and 25 have been deleted because claim 24 covers vesicles which are covered by process claims 16 and 18 to 23 while claim 25 is directed to the non-elected droplet claims.

Claim Rejections 35 U.S.C. §102

Claims 1-2, 6, 10, 16 and 21-24 stand rejected under 35 U.S.C. 102(b) as being anticipated by Eanes (Bone and Mineral 17, pp. 269-272, 1992) of record or Eanes (Calcif. Tissue Int (40 pp. 43-48, 1987). The Examiner asserts that Eanes in both publications discloses liposomes coated with calcium phosphate. The Examiner argues that the liposomes are suspended in sodium chloride and therefore the surface layer contains chloride ions as recited in claim 6.

Although it is possible that the liposomes of Eanes may be coated with calcium phosphate, the liposomes are in fact very different from those of interest to Applicant. This results from their very different purpose. Eanes has conducted experiments to investigate how the calcification of a liposome may be varied. In

contrast, Applicant is concerned with vesicles which can act more effectively as implants and for drug delivery.

The essential difference between the two types of liposome is that whereas the liposomes of Eanes contain calcium phosphate within them, Applicant's vesicles are substantially free of phosphate in the inner layer. This has been made clear in amended claim 1.

Thus Eanes indicates in the summary to the 1987 paper that "previous studies showed that in PS(-) liposomes, these latter losses [of calcium in solution] were due to calcium phosphate precipitation, with the precipitate confined to the interior of the liposomes when no external P_1 was present, but extending to outside the liposomes when the suspending medium was rendered metastable". Likewise the abstract of the 1992 paper ends with the statement "slow the expansion of the precipitation from inside to outside the liposome". It is clear, therefore, that the liposomes of Eanes contain calcium phosphate within them and, in certain circumstances, on the outside as well. It should also be noted that reference c to table 1 on page 270 of the 1992 paper states "onset of intra-liposomal [i.e. across the walls of the liposome to the inside] precipitation is immediate in all cases."

Eanes indicates that in some instances calcium phosphate is present on the outside of the liposomes. This occurs, according to page 47, left hand column of the 1987 paper "by the seeding action of intra-liposomal apatite crystals that have worked their way through the outer membranes into the external solution." In other words crystals of calcium phosphate nucleating within the liposomes extend through the liposome and puncture it.

It will be appreciated that such liposomes are useless for drug delivery and the like with which the Applicant is concerned. If the walls of the liposome are punctured by calcium phosphate crystals then any pharmaceutically active agent encapsulated by the liposome will leak out. Also the presence of calcium ions within the liposome is to be avoided because calcium ions are well known to complex with numerous compounds and they will complex with many pharmaceutically active compounds. It is believed to be clear, therefore, that Applicant's liposomes are different. This distinction has now been brought out in amended claim 1.

In addition new claim 34 specifies that the inner layer consists essentially of phospholipid and, optionally, at least one pharmaceutically active compound. Such a situation is discussed at page 4 lines 10 to 14. Of course other materials such as surfactants can be present to assist formation of the vesicles. Clearly the "consists essentially of" language for the inner layer excludes anything more than trace amounts of calcium phosphate.

Claim Rejections – 35 U.S.C. §103

Claims 7 to 12 stand rejected under 35 U.S.C. 103(a) as unpatentable over the two Eanes references. The Examiner admits that Eanes is lacking in the explicit teaching of the thickness of the coating of the vesicles by the calcium phosphate. This is agreed. The Examiner, though, adds that on page 270 Eanes appears to suggest that the coating on the external surface is time dependent and PL dependent and he therefore concludes that it would be obvious to one of ordinary skill in the art to obtain the vesicles with a desired coating thickness by varying the time and the selection of suitable phospholipids.

As argued above, Applicant's vesicles are fundamentally different from those of Eanes. As for the comments on the thickness of the coating, whereas it may be the coating is time dependant and PL dependent this does not address the question as to whether someone reading the Eanes paper would want a thickness as prescribed in claims 7 to 12. It is clear that the thickness of the layer is unimportant to Eanes investigations, whereas, naturally, it is important to Applicant where a uniform coating is desirable to encourage uniform bio-resorption and cellular interaction. In addition, if the coating is too thin, the liposome may not be completely coated whereas if the coating is too thick the vesicle becomes less usable as a pharmaceutical delivery device.

In paragraph 9 of the Official Action, claims 1-2, 6-16, 21-24, 26-29 and 31-33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over EP-0-479,582 of record in combination with either of Eanes and Chung (US-5,039,546).

The Examiner argues that EP discloses multi-laminar liposomes containing an antibiotic, these liposomes being suspended in hydroxyapatite for use with dental implants. The Examiner believes that what is lacking in EP is a teaching of coating the liposomes with apatite (calcium phosphate) instead of hydroxyapatite and also the attachment of the liposomes to a surface. The Examiner believes that these are made good by the Eanes articles which are concerned with the formation of calcium phosphate and by Chung which discloses that for dental implants one can coat with either hydroxyapatite or calcium phosphate.

The Examiner concludes, therefore, that it would have been obvious to replace hydroxyapatite by calcium phosphate in EP and that the coating of substrate would have been obvious in view of Chung although the Examiner admits that

Chung does not disclose specifically the sizes of the implants. The Examiner, believes, though, that these are within the skill of one in the art.

It is submitted that this argument does not actually advance the case for obviousness because there is no suggestion in EP that the liposomes should be formed onto a substrate. EP discloses a paste which is an admixture of liposomes and hydroxyapatite. There is nothing in EP to suggest that the hydroxyapatite should be formed on the liposomes, as the Examiner has admitted. EP is concerned with drug delivery whereas Eanes, as indicated above, is concerned with the way in which calcium phosphate is formed on liposomes. There is, therefore, no reason why one with skill in the art would combine these two teachings. Further it is clear that EP designs a paste to maintain the liposomes at the site for administration of the antibiotic. This could not be achieved if the liposomes merely had a layer of hydroxyapatite over them.

Additionally, Chung is concerned with increasing the stability of hydroxyapatite or calcium phosphate coatings on metal implants. It is not concerned with liposomes and although reference is made to "other calcium phosphate coatings" it is clear that the use of hydroxyapatite is preferred, there being no detailed discussion of any alternative. It is wrong, therefore, to say that calcium phosphate and hydroxyapatite are equivalent.

Claim 30 stands rejected under 35 U.S.C. 103(a) as being unpatentable over EP-0-479,582 of record in combination with either of Eanes and Chung further in view of Redepenning (US- 5,310,464).

Claim 30 concerns the electrolytic deposition of the coating comprising the vesicles on the conducting regions of the substrate.

Redepenning discloses an electrolytic deposition, it is true, but using not calcium phosphate but a specific calcium hydrogen phosphate, namely brushite which has the formula $CHPO_4 \cdot 2H_2O$. This is achieved from a solution containing Ca^{2+} and dihydrogen phosphate ions (see column 5, lines 8 and 9, 42 and 43). There is no reason, therefore, why one with skill in the art would adopt a similar electrodeposition process for depositing vesicles possessing a preformed calcium phosphate layer on their surface. The process is entirely different.

Conclusion

Under the circumstances, it is submitted that all the outstanding objections have been met and, therefore, an early allowance of this application is earnestly requested.

No other fees are believed to be needed for this amendment. However, if additional fees are needed, please charge them to Deposit Account No. 17-0055.

Respectfully submitted,
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Dated: February 7, 2003

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Version with markings to show changes made

-- 1. (Amended) A vesicle comprising

a) an inner layer which comprises a phospholipid, said inner layer being substantially free from calcium phosphate, and

b) an outer layer which comprises calcium phosphate. --

3. (Canceled.)

4. (Canceled.)

5. (Canceled.)

-- 6. (Twice Amended) A vesicle [or droplet] according to claim 1 wherein the outer layer further comprises ions selected from carbonate. hydrogen phosphate, chloride, fluoride or magnesium. --

-- 7. (Twice Amended) A vesicle [or droplet] according to claim 1 wherein the thickness of the outer layer is from 5 to 50 nm. --

-- 8. (Amended) A vesicle [or droplet] according to claim 7 wherein the thickness of the outer layer is from 5 to 20 nm. --

-- 9. (Amended) A vesicle [or droplet] according to claim 8 wherein the thickness of the outer layer is about 10 nm. --

-- 10. (Twice Amended) A vesicle [or droplet] according to claim 1 wherein the size of the vesicle [or droplet] is from 100 nm to 10 μm. --

-- 11. (Amended) A vesicle [or droplet] according to claim 10 wherein the size of the vesicle [or droplet] is at least 300 nm. --

-- 12. (Amended) A vesicle [or droplet] according to claim 11 wherein the size of the vesicle [or droplet] is at least 1 μm. --

-- 13. (Twice Amended) A vesicle [or droplet] according to claim 1 which further comprises a pharmaceutically active compound. --

-- 14. (Amended) A vesicle [or droplet] according to claim 13 wherein the pharmaceutically active compound assists the binding [of a coating comprising the vesicle or droplets] to bone, treats a specific bone disease or any diseased region adjacent to bone, or relieves pain. --

-- 15. (Amended) A vesicle [or droplet] according to claim 14 wherein the pharmaceutically active compound is selected from parathyroid hormone, vitamin D derivatives, bisphosphanates, bone morphogenetic proteins, analgesics, ^{32}P or ^{89}Sr containing compounds, indomethacin, prostoglandins, interleuken 6 inhibitors and antibiotics. --

17. (Canceled.)

-- 18. (Twice Amended) A process according to claim [17] 16 wherein the aqueous mixture further comprises an alcohol. --

24. (Canceled.)

25. (Canceled.)

- - 26. (Twice Amended) A solid substrate wherein regions of said substrate have attached thereto a layer comprising vesicles [or droplets] as claimed in claim 1 with other region or regions having no vesicles [or droplets] attached thereto. - -

- - 27. (Amended) A substrate according to claim 26 which comprises a surface layer comprising

[a)] electrically conducting and non-conducting regions [on its surface, and

b)] with a layer comprising vesicles [or droplets] on the conducting regions.

- -

- - 30. (Twice Amended) A process for preparing a substrate according to claim 26 which process comprises electrolytically depositing the coating comprising vesicles [or droplets] onto the conducting regions of the substrate. - -

31. (Canceled.)

32. (Canceled.)

33. (Canceled.)

- - 34. (New) A vesicle comprising

a) an inner layer which consists essentially of phospholipid and, optionally, at least one pharmaceutically active compound, and

b) an outer layer which comprises calcium phosphate. - -

- - 35. (New) A method of treating a bone disorder in a patient which comprises implanting in the patient a substrate as claimed in claim 26. - -

- - 36. (New) A method of delivering pharmaceutically active compounds to a patient which comprises implanting in the patient a substrate as claimed in claim 26 comprising one or more pharmaceutically active compounds. - -